Hormone Profiles in Humans Experiencing Military Survival Training

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Background: *Clinical models of the human response to intense, acute stress have been limited to laboratory settings or cross sectional characterizations. As a result, data about the sensitivity of the human neuroendocrine activation to realistic stressors of varying magnitudes are limited. The U.S. Army survival course offers a unique opportunity to examine, in a controlled manner, the human response to acute, realistic, military stress.*

Methods: *Salivary data were collected in 109 subjects at baseline during four stress exposure time points and at recovery. Serum data was collected at baseline and recovery in 72 subjects and at baseline and during stress exposure in a subgroup of subjects* (n = *21).*

Results: *Cortisol significantly increased during the captivity experience and was greatest after subjects' exposure to interrogations. Cortisol remained significantly elevated at recovery. Testosterone was significantly reduced within 12 hours of captivity. Reductions of both total and free T4 and of total and free T3 were observed, as were increases in thyrotropin.*

Conclusions: *The stress of military survival training produced dramatic alterations in cortisol, percent free cortisol, testosterone, and thyroid indices. Different types of stressors had varying effects on the neuroendocrine indices. The degree of neuroendocrine changes observed may have significant implications for subsequent responses to stress.* Biol Psychiatry 2000;47:891–901 © *2000 Society of Biological Psychiatry*

Key Words: Cortisol, testosterone, thyroid, military stress, posttraumatic stress disorder

Introduction

Investigations of mammalian stress physiology have shown that aversive physical stimuli (Opstad 1992, 1994) and psychological stimuli are independently capable of provoking significant neuroendocrine perturbations (Davis et al 1977; Mason 1968b; Sapolsky 1990; Schedlowski et al 1995). Because physical and psychological stress are an inevitable component of military life, this literature has been of considerable interest to researchers investigating normal and pathologic adaptations to stress (Friedman et al 1995).

The preclinical foundation for this investigation is the seminal work of Mason (1968a), which detailed the psychoendocrine responses of monkeys exposed to uncontrollable stress. Mason and colleagues demonstrated that exposure to uncontrollable stress resulted in a complicated and organized pattern of neuroendocrine responses also suggested that a more clear understanding of endocrine regulation and adaptation may be obtained by studying multiple hormone indices concurrently.

At the present time, however, there are few published reports describing the neuroendocrine responses of healthy soldiers confronting actual military stress. There are several reasons for this. First, many investigations have used types of laboratory stress that are not comparable to those experienced by soldiers during combat duty. For example, the cold pressor test (Bullinger et al 1984; Costa et al 1993), challenging mental tasks (Bohnen et al 1991; Caudell and Gallucci 1995), oral or written examinations, (Meyerhoff et al 1988; Wittersheim et al 1985) public speaking (Bassett et al 1987), and graphically unpleasant or gory films (Demyttenaere et al 1989; Hellhammer et al 1985; Zakowski et al 1992) have all been used in the laboratory to provoke the "acute stress response." Although capable of eliciting distress in subjects, it is doubtful that films, for example, elicit the sense of personal threat experienced by soldiers participating in actual military operations. As such, the dynamics and magnitude of hormone responses reported in these studies may not adequately characterize the human response to highly threatening stimuli.

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Second, while incorporating more intense, subjectively threatening stimuli (such as angioplasty or major surgery), other investigators have studied the acute stress response in medically compromised individuals (Brand et al 1995; Parker et al 1985; Schulte et al 1994). Although such research did provide important information about the range of endocrine responses to stressful, medically invasive events in medically compromised individuals, these studies have not characterized the responses of healthy soldiers.

Third, studies that have included psychologically stressful stimuli of a military nature (e.g., parachute jumping, operating aircraft, or actual combat-zone activity) have been limited by either small numbers of subjects (Chatterton et al 1997; Davis et al 1972; Rose et al 1969) nonuniform sampling times (Kreuz et al 1972; Miller et al 1970), or high rates of attrition (Bernton et al 1995). Although such studies have been instrumental in providing evidence that military-related stress may produce significant alterations in endocrine responding, they underscore the need for a more complete characterization of the impact of such realistic stress. This type of information is crucial to understanding the relationships between the stress magnitude of the psychological variables and individual differences in endocrine responses (Kok et al 1995). Data of this type are essential to evaluate such constructs as stress inoculation and stress sensitization in humans.

As a step toward a larger goal, the present investigation was modeled after that of Mason (1968a) and was designed to assess several neuroendocrine indices under relatively nonstressful conditions (baseline), to characterize potential alterations of these endocrine factors during acute, highly intense stress, and to evaluate these indices at recovery from stress exposure. A fourth goal was to determine whether subjective reports of stress are significantly related to endocrine profiles.

The U.S. Army's survival training course was selected because of its compatibility with the goals of this study. Highly realistic in nature and extraordinarily intense, U.S. Army survival training is among the most difficult and rigorous in the U.S. armed forces. It is designed to prepare soldiers to deal with situations that are beyond those in which they are routinely involved but for which they are considered at high risk, specifically, evading capture by the enemy and, when captured, surviving as prisoners of war.

Several factors make the survival course an ideal environment to study the effects of acute, realistic stress. First, subjects are drawn from a natural population of soldiers who are currently most likely to be exposed to extreme military operational stress. Second, the rate of attrition in survival training is extremely low (approximately 1 in 30). Third, the design and schedule of the training permits a stable baseline assessment, ensures a highly uniform application of stress across subjects, and provides the opportunity for a recovery-day assessment. Fourth, the highly realistic and intense nature of the stress experienced by subjects optimizes the possibility of documenting neuroendocrine responses that may have a meaningful relationship to the actual impact of highly intense stress on healthy humans. It is hoped that a more detailed characterization of the impact of extreme stress on neuroendocrine responses will enhance our understanding of the neuroendocrine abnormalities seen in individuals suffering from stress-related disorders such as posttraumatic stress disorder (PTSD; Southwick et al 1998).

Methods and Materials

The subjects of this study were 124 of 140 consecutively recruited active-duty male soldiers (age 28.8, SD = 5). Among these individuals, 60 subjects (48%) were married. The average number of years in the service before enrollment at the survival school was 7 (SD = 2.1). Before enrollment in this investigation, each completed inprocessing for the survival course. Recruitment of subjects was conducted by the principal investigator (CAM) at the U.S. Army John F. Kennedy Special Warfare Training Center and School, Fort Bragg, North Carolina. All subjects gave written, informed consent. As per course requirements, all subjects provided documentation of physical examination and medical clearance within 30 days of enrollment. All subjects were free of illicit substances. The 16 subjects who declined to enroll in the study did not differ as a group (in terms of age, rank, or military operational specialty) from those who did enroll. Eleven of the 16 stated they did not enroll because they were not confident that research information would remain separate from their military records. They worried that such information, if inadvertently included in their military records, might jeopardize their subsequent evaluations. The remaining five did not offer an explanation for refusing to participation in the study.

Baseline Psychological Assessment

Baseline subjective measures were collected in the classroom of the survival school training facilities. Subjects indicated the level of stress they were anticipating during the upcoming confinement phase of the course. To indicate their level of anticipatory stress, subjects used a 10-point Likert scale (0 = totally peaceful and relaxed; 10 = the most stressful experience ever, including combat). Finally, as noted above, independent variables, such as age, marital status, and number of years in the service, were assessed.

Baseline Hormone Assessment

Baseline measures were collected at the survival school training facilities. For all subjects, baseline salivary samples were obtained at 7:30 AM and at 5:00 PM on 2 consecutive days of classroom educational activities. Baseline serum samples were collected on the 3rd day of classroom instruction and coincided

with the second 5:00 PM saliva sample collection. Because of programmatic constraints, it was not possible to collect baseline serum samples from 19 subjects. Thus, these 19 were not included in the serum data analyses.

Stress Samples

At the conclusion of the didactic phase, soldiers entered the experiential phase of the survival course, consisting of an evasion phase and a captivity experience phase. During the evasion phase, subjects hid and slept during the day and conducted movements at night. During the captivity phase, subjects were given, in as highly realistic manner as possible, a captivity experience in the army's training laboratory (TL). In the TL, each individual was subjected to uncontrollable stress and attempted to avoid exploitation. Because of the classified nature of the course, a detailed description of the individual stressors is not possible. The challenges to subjects during the captivity experience are modeled from those experienced by American POWs in World War II, Korea, and Vietnam. Broadly speaking, these include interrogations and problem-solving dilemmas designed to test their ability to utilize and adhere to their training and a prescribed code of conduct.

The rigorous and realistic nature of the training restricted the manner and timing of data collection during the TL. Salivary sample collections were performed at specific time points previously identified by survival instructors (who were also previous participants) as ranging from moderately to extremely stressful: the time of capture (T1, approximately 7:45 AM); immediately following two different types of intimidating military interrogations (T2, approximately 12 hours postcapture; T3, approximately 18 hours postcapture); and 30 min after subjects experienced the dilemma of being led to believe that they were being released from their captivity experience, were detained from release, and then were actually released (T4, approximately 48 hours after T3). At time points T1, T2, and T3, saliva was collected by the investigators (CAM & GH). The cotton from the collection tube was placed in the subjects mouths, and the salivet tube was held up to the subjects' mouths to recollect the cotton and extra saliva. At time point T4 (and at baseline [B1–B4] and recovery [R1–R2]), subjects held the salivet collection tubules themselves.

Finally, serum samples were obtained on a subgroup of subjects ($n = 21$), immediately after their first highly intense interrogation (T2) in the TL. This coincided with the collection of their T2 salivary sample time point and permitted an assessment of the magnitude of serum hormone responses to the stress of interrogation.

The operating procedures and training standards of the U.S. Army, Navy, and Air Force survival schools are set and monitored by the Joint Services Survival Agency. This agency, comprised of both civilian and active duty scientists, is responsible for ensuring ethical, safe, and effective survival training of military personnel. Persons interested in training standards or interested in conducting a replication study are invited to contact the first author for a point of contact within the JFK Special Warfare Center and School.

Recovery Psychologic and Hormone Samples

At recovery, salivary samples were collected at 7:30 AM the day after the conclusion of the captivity experience and at 3:00 PM. The afternoon recovery day sampling time point was dictated by the survival course schedule and differed from the afternoon sampling time points at baseline by 2 hours. Just before donating the recovery saliva and serum samples, subjects once again completed the subjective stress scale. This time, subjects were instructed to rate how stressful they felt the confinement phase (TL) had been (0 = totally peaceful and relaxed, 10 = most stressful experience ever, including combat).

Serum Thyroid Hormones

Blood samples (10 mL) for thyroid hormone assays were collected and, after setting of the clot and centrifugation, the serum was divided into three 1.5 mL aliquots in small plastic vials and transported to our laboratory on dry ice where they were frozen at −70°C until assayed. Serum total T4, free T4, total T3, and thyroxine binding globulin (TBG) concentrations were measured by radioimmunoassay (RIA) procedures with the use of RIA kits (Incstar Corp, Stillwater, MN). The interassay coefficient of variation in our laboratory is 3.7% for total T4, 4.2% for free T4, 6.0% for total T3, and 3.0% for TBG. Serum free T3 concentrations were measured by an RIA kit procedure (Diagnostic Products Corp, Los Angeles). The interassay coefficient of variation in our laboratory is 2.7%. Serum thryrotropin concentrations were measured by a sensitive third-generation immunoradiometric assay kit (Incstar), and the interassay coefficient of variation is 4.0% in our laboratory.

Serum and Salivary Cortisol

Serum was collected as described above. Saliva was collected in Salivette tubes (Sarstedt, Newton, NC), centrifuged, and placed into two 1.5 mL plastic vials with pipets. The samples were shipped on dry ice to our laboratory and stored at −70°C until assayed. Serum and salivary cortisol were analyzed by RIA procedures (Incstar). The interassay coefficient of variation in our laboratory is 6.1%.

Serum and Salivary Testosterone

Serum and salivary testosterone were collected as described above. Serum and salivary testosterone concentrations were measured by RIA procedures (Diagnostic Products). The interassay coefficient of variation in our laboratory is 5.4% for total testosterone and 4.5% for free testosterone.

Psychological Data

A general linear model ANOVA was used to compare subjective stress ratings completed before and after exposure to the TL. Pearson correlation analyses were performed to detect whether there was a relationship between stress ratings and baseline stress or recovery hormone values, respectively. Pearson correlation analyses were also performed to evaluate the relationship between subjective stress ratings and the independent variables of

age, marital status and number of years in the service. Hierarchical regression analyses also were used to examine the cumulative and relative contributions of these independent variables and their interactions to the prediction of baseline, RTL, and recovery values for cortisol, testosterone, and thyroid hormones.

Hormone Data

The rigorous nature of survival training prevented some subjects from providing salivary or serum samples at various time points during the training. Because 19 subjects provided recovery serum data but were unable to provide baseline serum samples, they were not included in the serum analyses. Only subjects with both baseline and recovery samples ($n = 72$) or baseline and TL samples ($n = 21$) were included in serum analyses. Similarly, only subjects with saliva samples from at least 9 of the 10 saliva collection time points were included in the analysis. It was not possible to collect saliva samples at the time of "capture" (T1) in 20 subjects. Nonetheless, valid data were available from all other nine data collection time points in these subjects. Therefore, salivary data was analyzed with ($n = 109$) and without ($n = 89$) these 20 subjects. As a result, analyses of the larger group do not include the T1 time point, but those of the smaller group do include a T1 time point.

Salivary Data

Salivary data from subjects were compared using one-way repeated measures ANOVA to detect whether significant changes in salivary cortisol or testosterone occurred during survival training. When analyses were conducted on the sample of 109 subjects, the factors were mean baseline, T2, T3, T4, and mean recovery; for the sample of 89 subjects, an additional factor, T1, was included. Post hoc t tests were employed to determine how the various time points differed from one another.

Serum Data

Paired t tests were used to compare baseline and recovery serum hormone values. Paired t tests were also used when comparing the baseline and midpoint (TL) serum samples that were obtained from a subgroup of subjects ($n = 21$). Independent t tests were performed between the baseline serum hormone values of the larger sample ($n = 72$) and those of the subsample ($n = 21$) to determine whether the subgroup was representative of the larger group.

Results

Subjective Stress Scales

Before experiencing the TL, soldiers ($N = 94$) rated the anticipated level of survival school stress. The mean value was 6.3 (SD = 2.0). After experiencing the TL, subjects' subjective stress scores were noted to be increased. The mean value was 7.6 (SD = 1.9). General linear model ANOVA addressing this increase revealed significant within-subject and between-subject effects [$F(1,65) = 31.7$, $p < .0001$; $F(1,65) = 1020$, $p < .0001$]. No differences were observed in the subjective stress ratings, either before or after the TL, between the Special Forces soldiers and the general troop soldiers. No significant correlations were observed between subjective stress scores and hormone values at baseline, during stress, or at recovery. No significant correlations were observed between subjective stress scores and independent variables such as age, marital status, or number of years in the service.

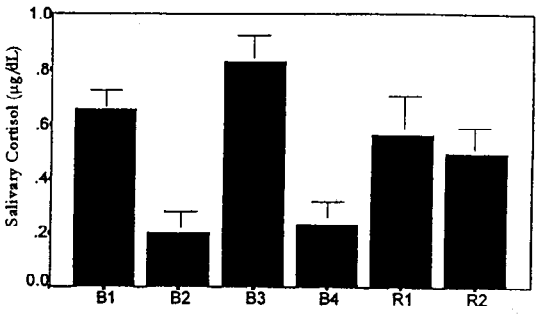

Figure 1. Diurnal variation of salivary cortisol at baseline and recovery. Two baseline sampling days: B1 and B3, 7:30 AM; B2 and B4, 5:00 PM. One recovery sampling day: R1, 7:30 AM; R2, 3:00 PM. $N = 109$.

Hormone Data

CORTISOL SALIVARY MEASURES. As depicted in Figure 1, subjects displayed normal diurnal variation of cortisol at baseline. As depicted in Figure 2 and Table 1, salivary cortisol significantly increased, compared with baseline, in response to survival training stress. Analyses of variance using the sampling time points available for the sample of 109 subjects (mean baseline, T2, T3, T4, mean recovery) indicated that both significant between-subject and within-subject effects were observed [$F(1,108) = 7.68$, $p < .0001$; $F(4,432) = 15.5$, $p < .0001$, respectively]. Similarly, analyses of variance of the sample of 89 subjects for whom a complete data set was available (mean baseline, T1, T2, T3, T4, mean recovery) also revealed significant between-subject [$F(1,88) = 120.6$, $p < .0001$] and within-subject effects [$F(5,435) = 16.9$, $p < .0001$]. Thus, the inclusion or exclusion of the 20 subjects did not affect any of the results. Post hoc analyses indicated that, compared with baseline, statistically significant increases in salivary cortisol occurred at the time of capture [T1; $T(1,88) = 6.8$, $p < .0001$], immediately following the first interrogation [T2; $T(1,108) = 5.6$, $p < .0001$], following the second interrogation [T3; $T(1,108) = 4.2$, $p < .0001$], and at the conclusion of the captivity experience [T4; $T(1,108) = 6.5$, $p < .0001$]. All

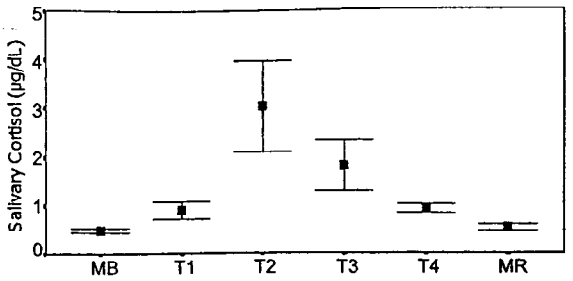

Figure 2. Salivary cortisol (mean and SEM) before, during, and after survival school stress. Salivary data of soldiers during mean baseline (MB), time of capture (T1), time of interrogations (T2 and T3), release (T4), and mean recovery (MR). $N = 109$.

comparisons between individual time points are noted in Table 1.

As shown in Figure 1, and unlike during baseline, no diurnal variation of salivary cortisol was observed at recovery. In addition, comparisons of the salivary cortisol values collected at time point B4 to salivary cortisol values collected at R2, revealed that salivary cortisol values remained significantly elevated 24 hours after cessation of stress exposure [0.23 ug/dL vs. 0.47 ug/dL; $T(1,111) = 16$, $p < .0001$].

SERUM CORTISOL MEASURES. As shown in Table 2, paired t tests indicated that, compared to baseline, serum cortisol was significantly elevated 24 hours after the conclusion of survival training [$N = 72$; $T(1,70) = 9.8$, $p < .0001$]. In a subsample of subjects ($n = 21$) whose serum cortisol values were obtained immediately following exposure to intense psychological interrogation paired t tests indicated that postinterrogation values (T2, TL) were also significantly greater than baseline cortisol values [$T(1,20) = 13.0$, $p < .0001$] suggesting that the stress of military interrogation significantly increased serum cortisol. Independent t tests did not show significant differences in baseline cortisol between the subgroup ($n = 21$) and the larger group ($n = 72$).

SALIVARY-SERUM CORTISOL RATIOS. At baseline, the percent free cortisol (as reflected by the salivary to serum cortisol ratio) was noted to be 3%. During and after exposure to stress, the percent free cortisol increased to values of 5% and 4%, respectively. General linear model analysis of variance indicated that compared with baseline, significant within-subject and between-subject increases in percent free cortisol were observed during stress [$F(1,19) = 94.4$, $p < .0001$; $F(1,19) = 507.5$, $p < .0001$] and at recovery [$F(1,70) = 6.1$, $p < .02$; $F(1,70) = 573.7$, $p < .0001$, respectively].

TESTOSTERONE SALIVARY MEASURES. As shown in Figure 3, subjects displayed some variation of salivary testosterone at baseline. As shown in Figure 4 and Table 1, compared with mean baseline, salivary testosterone significantly decreased in response to survival training stress. Analyses of variance using the sampling time points available for the sample of 109 subjects (mean baseline, T2, T3, T4, mean recovery) indicated that both significant between-subject and within-subject effects were observed [$F(1,88) = 673$, $p < .0001$; $F(5,440) = 40$, $p < .0001$]. Similarly, analyses of variance of the sample of 89 subjects who had complete data (mean baseline, T1, T2, T3, T4, mean recovery) also revealed significant between-subject [$F(1,108) = 1042$, $p < .0001$] and within-subject effects [$F(4,432) = 66$, $p < .0001$]. Thus, the inclusion or exclusion of the 20 subjects did not alter the findings. Post hoc analyses indicated that, compared with mean baseline, statistically significant decreases in salivary testosterone occurred at the time of capture [T1; $T(1,88) = 7.5$, $p < .0001$], immediately following the first psychological interrogation [T2; $T(1,108) = 10.2$, $p < .0001$], following the second psychological interrogation [T3; $T(1,108) = 14.9$, $p < .0001$], and at the conclusion of the captivity phase [T4; $T(1,108) = 16.9$, $p < .0001$]. As seen in Table 1, the greatest reductions in salivary testosterone were observed at time points T3 and T4. Although these time points did not differ significantly from one another, each was significantly reduced compared with T1 [$T(1,88) = 3.85$, $p < .0002$; $T(1,88) = 5.6$, $p < .01$, respectively] and compared with T2 [$T(1,108) = 4.7$, $p < .0001$; $T(1,108) = 5.7$, $p < .001$, respectively]. Statistically significant differences were also observed between mean baseline and mean recovery values of salivary testosterone [$T(1,108) = 9.48$, $p < .0001$]. As shown in Figure 3,

Table 1. Mean and SD in Salivary Cortisol and Salivary Testosterone during and after Training

	Mean baseline	T1[a]	T2	T3	T4	Mean recovery
Cortisol (µg/dL)	0.49 (± 0.30)[c]	0.92 (± 0.53)[b,d]	2.99 (± 4.77)[b,e]	2.06 (± 4.0)[b,e]	0.90 (± 0.50)[b,d]	0.51 (± 0.29)[c]
Testosterone (ng/dL)	15.0 (± 4.7)[c]	10.5 (± 5.0)[b,d]	10.6 (± 4.6)[b,d]	8.70 (± 4.2)[b,e]	8.62 (± 3.7)[b,e]	10.7 (± 4.9)[b,c]

[a]Because of programmatic constraints, it was not possible to collect saliva samples from 20 subjects at the T1 time point. Therefore, the number of subjects available for analysis at T1 was 89. At all other time points, the number of subjects was 109.

[b]Analyses of variance indicated significant differences from mean baseline ($p < .0001$).

[c,d,e]Values with the same letters indicate no significant difference from one another in post hoc comparisons.

Table 2. Changes in Serum Cortisol, Testosterone, and Thyroid Indices during and after Training

	Mean baseline (n = 72)[a]	Mean recovery (n = 72)	Mean baseline (n = 21)[a,b]	During stress (T2) (n = 21)
Cortisol (μg/dL)	8.4 (± 3.1)	13.1 (± 3.6)[c]	9.3 (± 2.9)	33.6 (± 8.5)[c]
Total testosterone (ng/dL)	430 (± 147)	218 (± 91.2)[c]	415 (± 108)	199.1 (± 126)[c]
Free testosterone (pg/mL)	14.1 (± 3.8)	5.2 (± 2.1)[c]	14.9 (± 2.7)	7.04 (± 3.9)[c]
Total T3 (ng/dL)	172 (± 23.5)	133 (± 19.9)[c]	183.5 (± 21.6)	132 (± 12.1)[c]
Free T3 (pg/mL)	3.1 (± 0.5)	2.6 (± 0.54)[c]	3.5 (± 0.6)	2.64 (± 0.4)[c]
Total T4 (μg/dL)	8.0 (± 1.4)	7.6 (± 1.2)[d]	8.2 (± 1.3)	8.4 (± 1.1)
Free T4 (ng/dL)	1.6 (± 0.2)	1.51 (± 0.2)[c]	1.69 (± 0.2)	1.51 (± 0.2)
TSH (μIU)	1.64 (± 0.69)	2.46 (± 1.2)[c]	1.41 (± 0.7)	1.96 (± 1.3)

TSH, thyrotropin.

[a]The survival school program only permitted two venipunctures per subject. Seventy-two subjects were sampled at baseline and 24 hours after the conclusion of the course. Twenty-one subjects were sampled at baseline and immediately after exposure to interrogation during the captivity phase (training laboratory) of the course. Analyses of variance indicated significant differences from mean baseline ($p < .0001$).

[b]No significant mean baseline differences when compared with those of the large group (n = 72) using independent t tests.

Analyses of variance indicated significant differences from mean baseline: [c]$p < .001$; [d]$p < .01$; [e]$p < .06$.

normal diurnal variation of salivary testosterone was not observed at recovery.

SERUM TESTOSTERONE MEASURES. As shown in Table 2, paired t tests revealed that serum total and free testosterone values were markedly reduced compared with baseline values, after exposure to stress. These reductions were highly significant and were confirmed statistically [$T(1,71) = 14.5$, $p < .0001$; $T(1,71) = 21.4$, $p < .0001$, respectively]. Paired t tests within the subgroup also revealed that serum total and free testosterone values were markedly reduced, compared with baseline values, during exposure to the stress of the training laboratory [$T(1,19) = 7.9$, $p < .0001$]. Independent t tests comparing baseline serum total and free testosterone values of the sub-group (n = 21) to to those of the larger group (n = 72) did not reveal significant differences.

THYROID. As shown in Table 2, significant reductions were observed at recovery in serum total T3 [$T(1,71) = 10.7$, $p < .0001$], serum free T3 [$T(1,71) = 7.0$, $p < .001$], and serum total T4 [$T(1,71) = 3.44$, $p < .001$]. Only a trend toward significant reduction was observed for free T4 [$T(1,71) = 1.95$, $p < .06$]. Recovery TSH was significantly increased compared with baseline [$T(1,71) = 6.1$, $p < .0001$]. Independent t tests did not show significant differences in serum total or serum free T3 between the TL subgroup and the recovery group.

Hierarchical Regression Analyses

The cumulative and relative contributions of age, marital status, number of years in the service, as well as their interactions to the prediction of baseline, stress, and recovery values for each of the hormones, were examined through hierarchical regression analyses. No significant interactions were observed.

Discussion

The realistic stress of the training laboratory produced rapid and profound changes in cortisol, testosterone, and thyroid hormones. These alterations were of a magnitude that cannot be accounted for by sleep deprivation (Gonzalez-Santos et al 1989) and are comparable to those

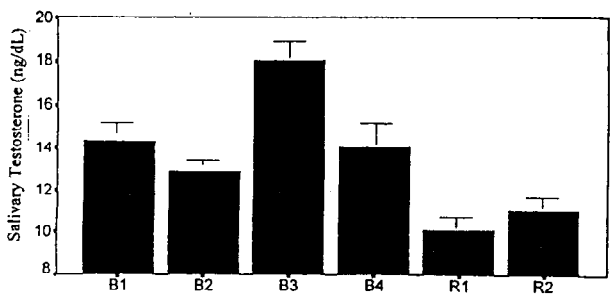

Figure 3. Salivary testosterone at baseline and recovery. Two baseline sampling days: B1 and B3, 7:30 AM; B2 and B4, 5:00 PM. One recovery sampling day: R1, 7:30 AM; R2, 3:00 PM. N = 109.

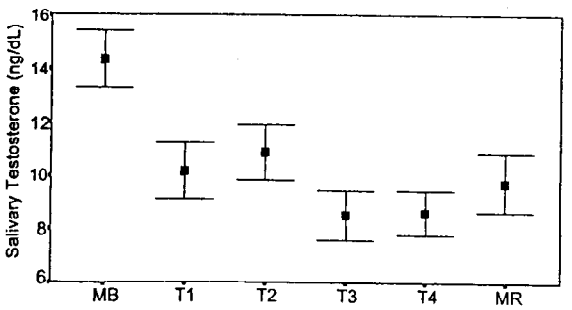

Figure 4. Salivary testosterone (mean and SEM) before, during and after SERE stress. Salivary data of soldiers during mean baseline (MB), time of capture (T1), time of interrogations (T2 and T3), release (T4), and mean recovery (MR). N = 109.

documented in individuals undergoing physical stressors such as major surgery or actual combat. The current data also provide robust evidence that the availability of unbound or free, cortisol is significantly enhanced by exposure to stress and that individuals differ significantly in the degree to which free cortisol is made available to them during exposure to stress. To the best of our knowledge, this is the first demonstration that psychological stress significantly increases the level of bio-available cortisol in humans (Kirschbaum et al 1999). In addition, the present study provides robust evidence that the magnitude of hormone responding increased with both the magnitude and the duration of the stressor. Finally, the current data are compatible with the work of Mason (1968a) and suggest that the U.S. Army survival school may be a valid, naturalistic model for the study of unavoidable stress in humans.

Glucocorticoids, such as cortisol, are essential in mammalian adaptation to stress. They mobilize energy, suppress nonessential anabolic activity, and increase cardiovascular tone. At baseline, subjects exhibited normal levels of cortisol; in response to the intense stress of captivity, glucocorticoids levels significantly increased and were greatest after exposure to the stress of military interrogations. Serum cortisol levels measured during stress (33.6 μg/dL, or the equivalent of 927 nmol/L) were equal to or greater than those measured in individuals undergoing major surgery (717 nmol/L) (Parker et al 1985), continuous and exhausting physical exercise corresponding to 35% VO_2 max (731 nmol/L; Opstad 1994), flying military aircraft (221 nmol/L; Leedy and Wilson 1985; Leino et al 1995), or skydiving (450 nmol/L; Chatterton et al 1997).

Cortisol is secreted in an unbound state; however, it circulates largely bound to high-affinity sites on corticosteroid binding globulin (CBG). Although bound cortisol is biologically inactive, approximately 5–10% of the steroid may circulate in the free (non–protein bound) state. This free fraction is biologically active, relates the physiologic effects, and is efficiently dialysed into saliva. It generally is accepted that salivary cortisol levels represent approximately 3% of the total plasma or serum concentration.

Statistically significant within-subject and between-subject differences were observed in the saliva-serum ratios of cortisol during exposure to stress and at the recovery time point. The percent free cortisol at baseline (2%) increased to 5% during exposure to stress and was noted to be 4% at the recovery time point. These data suggest that the availability of free cortisol (i.e., biologically active steroid) is increased by exposure to acute stress. In addition, individuals vary significantly in the degree to which exposure to stress increases the availability of free cortisol.

Although previous investigations have demonstrated that factors such as menstrual-cycle phase or the use of oral contraceptive may significantly affect the percent free cortisol (presumably through the influence of such factors on CBG levels), to our knowledge, this is the first report of a stress-facilitated increase in percent free cortisol. Percent free cortisol data may provide a fruitful way of evaluating individual differences in HPA reactivity to stress. In addition, these data underscore the need for multiple assessment time points, as well as serum and saliva data, to determine range of biologically active steroid that is available to an individual.

The stress-induced elevations of cortisol seen in the present study are of a magnitude compatible with levels of glucocorticoids known to be associated with immunosuppression (Bernton et al 1995; Shippee et al 1994). Indeed, glucocorticoid-induced immunosuppression may explain some reports by the survival school medical staff of frequent episodes of cellulitis in many participants (unpublished observations). In addition, the stress-induced levels of cortisol during the captivity experience are compatible with levels known to be capable of producing declarative memory deficits in humans (Kirschbaum et al 1996). Glucocorticoid-induced declarative memory deficits may explain, in part, reports by survival school participants that they cannot remember many aspects of their experience (C.A. Morgan et al, unpublished data, 2000). Clearly, the data obtained in this study do not provide direct evidence of either stress-induced immunosuppression or memory deficits. Nonetheless, the magnitude of the hormone alterations demonstrated by subjects in this study establish that such phenomena are realistic possibilities. Clearly, these issues warrant further study because they may affect the health of soldiers.

Consistent with the findings of Opstad (1994), diurnal variation of cortisol appears have ended 24 hours after the conclusion of stress exposure. Circadian rhythmicity of hypothalamic neurosecretion is influenced highly by both the sleep-wake cycle and the local concentration of steroids. It seems likely that factors such as sleep deprivation and increased levels of circulating glucocorticoids contributed to the lack of diurnal variation.

Mean baseline serum testosterone (430 ng/dL) was low compared with baseline values documented in active duty soldiers initiating U.S. Army ranger training (650 ng/dL) (Bernton et al 1995). Many soldiers participate in field training before their arrival at survival school; therefore, it is possible that overall lower baseline levels are reflective of the impact of this pattern training. In future investigations, assessment of subjects' training schedules before their participation in the course may help clarify the relationship between chronic military training and baseline testosterone levels.

Significant reductions of total and free testosterone were observed at the time of capture and during the TL phase of the course. Because no salivary or serum samples were collected during the 48-hour evasion phase that preceded the captivity phase, the exact time course for the reduction in testosterone before the subjects' capture is not known. Salivary and serum samples from the TL provide robust evidence that castrate levels of testosterone may be observed within 12 hours of captivity (within 72 hours of baseline). It is possible that some reduction of testosterone was produced by the nocturnal activity of the evasion phase; however, it is more likely that the anticipatory anxiety about being captured contributed to the reduction seen at the capture time point (Schulz et al 1996). The reductions in testosterone cannot be explained solely by the evasion phase because significant reductions of testosterone continued to occur during the captivity phase. Stress-induced reductions in testosterone are equal to or greater than those demonstrated after 8 weeks of chronic and extreme physical stress (Moore et al 1992) and after 1 week of 35% VO_2 max exertion (Opstad 1992, 1994). It is extremely unlikely that alterations of this magnitude can be explained by caloric deprivation alone because previous investigations have reported that total testosterone in humans was not affected by 1 full week of controlled fasting (Tegelman et al 1986).

The primate testicular axis is highly sensitive to the effects of both physical and psychological stress and is extraordinarily complex (Sapolsky 1991). It generally is believed that that the stress-induced inhibition of the reproductive axis is mediated via CRF release, glucocorticoids, and catecholamine levels (Cumming et al 1983; Eik-Nes 1971; Levin et al 1967; Opstad 1992). In vitro studies suggest that another possible explanation for the stress-induced reduction in testosterone is the stress-induced release of central opiates that, in turn, decrease lutinizing hormone (LH) by diminishing hypothalamic-pituitary portal concentrations of gonadotropin releasing hormone (GnRH) and GnRH release (Sapolsky 1991). In light of these data, future studies might examine the stress-protective effects in humans of opiate-blocking agents. The TL (captivity) phase of the course included fasting, sleep deprivation, and acute unpredictable stress, all of which may affect the hypothalamic-pituitary-thyroid (HPT) axis in humans. Short-term caloric deprivation alters the HPT in humans, including decreased circulating levels of serum triiodothyronine (T3) and suppression of serum thyrotropin (TSH; Hughes et al 1984; Merimee and Fineberg 1976; Spencer et al 1983). Kinetic studies have demonstrated that the decrease in serum T3 concentration reflects a decrease in peripheral generation of T3 from T4, rather than a change in its metabolic clearance rate (Larsen et al 1992). The high levels of cortisol during the interrogations also may have suppressed T3 because significant decreases in T3 are induced by pharmacologic doses of glucocorticoids in both normal and hyperthyroid patients (Larsen et al 1992). On the other hand, sleep deprivation, physical activity, and acute unpredictable stress influence the HPT axis by significantly increasing T3 and TSH (Baumgartner et al 1990; Gary et al 1996; Goichot et al 1994). In this study, significant decreases were observed in total and free T3 from baseline to recovery. Within the context of multiple, conflicting forces on the HPT axis during the RTL, it is likely that caloric deprivation was the strongest factor influencing the regulation of T3.

Total T4 was mildly increased during the TL compared with baseline and then significantly decreased at recovery. Free T4 was also reduced at recovery. Because inhibition of the peripheral conversion of T4 to T3 is responsible for the sharp drop in T3 during fasting, the slight increase of total T4 during the TL could reflect a buildup of unused substrate for the conversion, which during recovery (and refeeding) is once again used as a substrate. Therefore, T4 may be reduced at recovery as its conversion to T3 resumes. TSH increased from baseline to recovery with an intermediate increase during the TL. This increase is not easily explained. TSH is suppressed during fasting and increases during sleep deprivation and stress. Perhaps the sleep deprivation and stress of the TL overcame the suppressive effect of fasting on TSH production. At recovery, after refeeding and rest, TSH levels increased, reflecting a normal response to the low serum T3 levels.

Of note, baseline mean serum total T3 (177 ± 23.5 μg/dL) free T3 (3.1 ± 0.5 pg/mL) values were somewhat elevated in SERE subjects compared with civilian norms (127 ± 5 ng/dL and 2.64 ± 0.1 pg/mL, respectively; Mason et al 1973, 1994). In fact, the mean baseline serum total T3 value was similar to the elevated total T3 levels found in combat veterans with PTSD (Mason et al 1994; Wang and Mason 1999). The higher baseline T3 may be related to the anticipation of the extremely intense TL experience and the fact that many of the soldiers have had previous combat experience. Consistent with reports of elevated T3 in combat veterans, serum free T3 was especially elevated in two subjects who identified themselves as having combat-related PTSD (3.67 pg/mL and 3.83 pg/mL).

At this point, it is unclear how best to characterize the TL stress. Whether the stress experienced by subjects during "capture" and during interrogation is comparable to preclinical unavoidable stress is not clear. Because preclinical evidence suggests that the manner in which stress affects neuroendocrine responses depends on whether the stress is perceived by the animal as avoidable (for example, whether an animal perceives a way to escape from or control the stress by pushing a bar or lever, etc.) or

unavoidable (the animal is neither able to avoid nor manipulate the aversive stimulus), several comments are in order.

Unavoidable stress is thought to produce more widespread physiologic changes than is controllable stress, for example, greater alterations in cortisol responding (Dess 1983), gastric ulcers (Weiss 1971), immunosuppression (Maier and Laudenslager 1985), and reductions in CNS monoamines (Anisman 1978; Anisman and Sklar 1979). Although several of these dependent measures were not assessed in this study, others were. It is noteworthy that the neuroendocrine alterations of cortisol and testosterone induced by brief exposure to TL stress equaled or exceeded those seen in soldiers exposed to 8 weeks of ranger training. In ranger training, stress may be considered avoidable in that soldiers are able to actively manipulate their environment to cope.

In one sense, subjects experienced circumstances in the TL over which they had no physical or verbal control. This is to say that it was not possible for subjects to exert an influence over the applied stress by taking a physical or verbal course of action. Indeed, the rules of the survival training stipulate that physically resisting or "running away" from the confinement phase will result in expulsion from the course. During this phase of the training, participants are expected to apply what they have been taught in the classroom phase of training to cope with circumstances that are beyond their direct control. Performance feedback is not explicit during the TL, and each student must privately appraise how he or she is coping. Explicit feedback is reserved for the debriefing phase of the recovery phase.

As alluded to above, the only course of action by which a student may control the situation is to withdraw from the course either by explicitly stating that he or she will no longer continue training or by violating the rules surrounding the parameters of the course. The implications of the decision to quit the course are tremendous and are likely to result in ineligibility for special operations missions. For most participants, the choice to quit survival training (not participation in the study) is a decision that will result in a loss of leadership potential and a loss of a career that they have been cultivating for more than 5 years in active duty service.

The present study has certain limitations. First, most soldiers (but not all) who participate in survival school training are considered "stress hardy" by military standards. Therefore, the neuroendocrine responses documented here may be an underestimate compared with those that might be found in stress-naive populations. Second, although there were few dropouts ($n = 4$) in this study, a number of cases were dropped from the analyses because of missing data points. Missing salivary data were often the result of the subjects being unable to produce saliva, probably because of high levels of sympathetic activity. Therefore, our data may underestimate slightly the magnitude of some stress responses. Third, it is possible that the baseline assessment in this sample is not a true baseline because the classroom phase is undoubtedly stressful to some individuals. Survival school participants are aware that the experiential phase will follow the didactic phase, and many experienced anticipatory anxiety. This raises the possibility that realistic stress may exert a greater impact on baseline hormone values than is portrayed in this study (Schulz et al 1996). Subjects are aware that they will not die as a result of interrogation stress, but they also are aware that training-environment stress and exposure the elements does place them at high risk for potentially life-threatening medical events. Fourth, recovery-day assessment occurred on one day, 24 hours after the cessation of stress, limiting data about the time course of neuroendocrine recovery from acute stress. Nevertheless, these data do indicate that neurohormones are moving toward baseline values within 24 hours after the cessation of stress. Fifth, the current data do not explain the large between-subject differences in hormone responses to stress. Clearly, survival school training may offer a productive model for the future study of the significance of such individual differences and their long-term consequences.

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